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Dkt. 60623-A/JPW/GJG/DJK

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Adrian Gilbert, et al.

Serial No. : 09/788,131 Examiner: F. VanderVegt

Filed : February 16, 2001 Group Art Unit: 1644

For : ORAL, NASAL AND PULMONARY DOSAGE FORMULATIONS OF COPOLYMER 1

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September 24, 2004

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SIR:

COMMUNICATION IN RESPONSE TO JULY 19, 2004 ADVISORY ACTION AND PETITION FOR THREE-MONTH EXTENSION OF TIME

This Communication is being submitted in response to the July 19, 2004 Advisory Action issued by the United States Patent and Trademark Office in connection with the above-identified application. The period of reply to the July 19, 2004 Advisory Action was set to expire three months from the mailing date of the March 24, 2004 final Office Action issued in connection with the subject application, i.e. June 24, 2004. Applicants hereby petition for a three (3) month extension of time to bring the subject application in to pending status upon the filing of this communication. The fee for a three (3) month extension of time is $950.00 and a check in that amount is enclosed. With the three-month extension, the period for reply to the July 19, 2004 Advisory Action expires six months from the

mailing date of the March 24, 2004 final Office Action, i.e. September 24, 2004, and this Communication is timely filed.

In the July 19, 2004 Advisory Action, the Examiner entered the applicants' June 22, 2004 Amendment. However, the Examiner maintained the obviousness-type double patenting rejections of claims 1, 3-35, 37-43, 50-54 and 61-66 over U.S Patent No. 6,214,791 to Arnon, et al., ("the '791 patent") in view of the respective secondary references (i.e., U.S. Patent No. 6,024,981 to Khankari, et al., ("the '981 patent"); U.S. Patent No. 5,965,600 to Sato, et al., (the '600 patent); and U.S. Patent No. 6,162,800 to Dolle, et al. ("the '800 patent") for the reasons of record.

Obviousness-type Double Patenting

In response, applicants point out that claim 1 recites "an amount of microcrystalline cellulose in excess of 50 % by weight of the composition" and that none of the Examiner's cited references teach or suggest, implicitly or explicitly, making a pharmaceutical composition which comprises glatiramer acetate and "in excess of 50 %" microcrystalline cellulose by weight.

In fact, as detailed below, none of the cited references combines glatiramer acetate and microcrystalline cellulose in any amount. Moreover, none of the cited references discloses use of microcrystalline cellulose in excess of 50% by weight in combination with any active ingredient. Finally, none of the cited references discloses the advantageous dissolution properties of formulations of glatiramer acetate with microcrystalline cellulose in excess of 50%.

Glatiramer Acetate and Microcrystalline Cellulose

The Examiner has acknowledged on page 4 of the March 24, 2004 final Office Action that the '791 patent does not disclose formulating glatiramer acetate with microcrystalline cellulose. The Examiner merely concluded that because microcrystalline cellulose is a "well-known" excipient, its combination with glatiramer acetate would have been *prima facie* obvious. Presumably, the Examiner would agree that lactose monohydrate is no less "well-known" as an excipient. However, applicants have shown in the subject application that not all "well-known" excipients can be formulated with glatiramer acetate. Specifically, Experiment 1C of the subject application shows that lactose monohydrate was discovered to have long-term incompatibility with glatiramer acetate (see page 20, lines 14-20 of the subject application). Microcrystalline cellulose, on the other hand, did not cause the problems resulting from the use of lactose monohydrate. Clearly, selecting the appropriate excipient for use with glatiramer acetate was not merely a matter of selecting a "well-known" excipient.

Microcrystalline Cellulose in Excess of 50%

Even if one assumes that selection of microcrystalline cellulose for use with glatiramer acetate was *prima facie* obvious, which it is not, none of the cited references teach or suggest using in excess of 50% by weight of the microcrystalline cellulose. This element of the applicants' claims is simply not found in any of the cited references.

Applicants respectfully submit that the Examiner has misconstrued the language of the '981 patent. Specifically, the Examiner supported the instant rejection by relying on the

paragraph which begins on column 13, line 60 and ends on column 14, line 2 of the '981 patent. This paragraph fails to support the Examiner's position. In fact, this paragraph confirms that microcrystalline cellulose was normally not used in excess of 50% in the prior art.

The first sentence of the above mentioned paragraph states, "[t]he conventional range of non-effervescent disintegrant agents used in conventional tablets can be as high as 20%."(emphasis added). Clearly, this defines an upper limit for the use of disintegrant agents in general, of which microcrystalline cellulose is an example.

The second sentence states, "[h]owever, generally, the amount of disintegration agent used ranges from between about 2 and about 5%, according to the Handbook of Pharmaceutical Excipients." (emphasis added). This sentence clearly provides the typical range of microcrystalline cellulose that was used in the art.

The third sentence then teaches that, "[u]nderstandably, however, when a rapidly disintegrating dosage form is envisioned, the relative proportion of disintegration agent used will be increased." This third sentence must be taken in the context of the first sentence, which provides an upper limit of 20% for the use of microcrystalline cellulose, and the second sentence, which provides the typical range of 2-5%. That is, the '981 patent teaches to one skilled in the relevant art that using 2-5% would be normal, but if rapid disinitegration is desired, one could increase the percentage of microcrystalline cellulose to the 20% upper limit. The

rationale for a different interpretation of this paragraph has not been set forth.

The fourth sentence reinforces this upper limit by stating "Cousins et al., for example, requires from about 6.1 to about 13.3% reticulated PVP, as described in its various examples." By providing examples of compositions with amounts of disintegrant in the range of about 6.1% to about 13.3%, i.e. less than 20%, the upper limit defined in the first sentence is reinforced. In fact, no amount above 20% of any disinitegrant is taught in the '981 patent.

Accordingly, one skilled in the relevant art would find no suggestion or motivation in the '981 patent to prepare a composition with greater than 20% of any disintegrant, let alone a composition with an amount of microcrystalline cellulose in excess of 50% by weight of the composition.

Advantages of Microcrystalline Cellulose for Glatiramer Acetate Dissolution

Even if one assumes that 1) selection of microcrystalline cellulose for use with glatiramer acetate was *prima facie* obvious (which it is not) and 2) the Examiner's interpretation of the '981 patent is correct (which it is not), there is still no teaching or suggestion in the any of the cited references that microcrystalline cellulose in excess of 50% provides the advantageous dissolution characteristics of glatiramer acetate formulations described in the specification. The use of microcrystalline cellulose in excess of 50 % by weight results in pharmaceutical compositions with excellent flow and mixing characteristics, improved dissolution and improved stability over that which would have

been expected based on the properties of glatiramer acetate (see page 37, lines 17-32 of the subject application). Furthermore, based on the properties of glatiramer acetate, it was unexpected that the formulation with microcrystalline cellulose, particularly in excess of 50 %, would have any, much less significantly improved pharmaceutical properties suitable for oral administration (see page 38, lines 1-13 of the subject application). For example, the claimed formulation has an advantageous property in that it allows for matching *in vitro* dissolution profiles of the tablet that contains 5 mg of glatiramer acetate with the tablet that contains 50 mg glatiramer acetate as shown in Figure 3. Specifically, and unexpectedly, even though the tablet containing 50 mg of glatiramer acetate is four times the weight of the tablet containing 5 mg of glatiramer acetate (see page 24, Table 5), both tablets have similar dissolution profiles (see page 37, line 29 to page 38, line 13). It is unexpected based on the prior art that the use of microcrystalline cellulose in excess of 50 % by weight will provide such advantageous properties.

Therefore, a pharmaceutical composition comprising glatiramer acetate and microcrystalline cellulose in excess of 50% by weight of the composition is not *prima facie* obvious in view of the cited prior art. Accordingly, applicants request that the Examiner reconsider and withdraw the obviousness-type double patenting rejection of claims 1, 3-35, 37-43, 50-54 and 61-66 over U.S Patent No. 6,214,791 to Arnon, et al., in view of U.S. Patent No. 6,024,981 to Khankari, et al.,; U.S. Patent No. 5,965,600 to Sato, et al.,; and U.S. Patent No. 6,162,800 to Dolle, et al.

No fee other that the $950.00 fee for the three-month extension is deemed necessary in connection with the filing of this Communication and a check in that amount is enclosed. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Gary J. Gershik 9/24/04

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